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Regioselective Alkylation of Heteroaromatic Compounds with 3-Methyl-2-Quinonyl Boronic Acids

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ABSTRACT

Reactions of heteroaromatic compounds with 3-methyl substituted 2-quinonyl boronic acids proceeded by 1,4-addition followed by spontaneous protodeboronation, leading directly to the Friedel−Crafts alkylation products instead of the commonly observed alkenylation derivatives resulting from quinones. The boronic acid acts as a temporary regiocontroller, making the system a highly reactive quinone equivalent and opening a direct access to 5,5-disubstituted cyclohexene-1,4-diones.

The Lewis acid catalyzed Friedel−Crafts (FC)[1,2] reaction of aromatic systems with α,β-unsaturated carbonyl compounds is one of the most powerful C−C bond-forming processes in organic synthesis, giving rise to the alkylation products resulting from the 1,4-conjugate addition. In sharp contrast, the FC reactions of heterocyclic compounds, such as indole with quinones, are a formal aromatic alkenylation, because the initial 1,4-addition product spontaneously enolizes to an aryl substituted hydroquinone, which usually undergoes in situ oxidation to the quinone, with the starting quinone or an additional reagent acting as an oxidant (Scheme 1).[3−5] When the electrophiles are substituted benzoquinones, the regioselectivity of the FC reaction is highly dependent on the type of substituent on each double bond (R). With dialkyl substituted (2,5- or 2,6-) quinones, the reaction generally occurs at the unsubstituted position, to give a quinone having a heteroaromatic substituent, after the aromatization/oxidation steps. Despite the significance of the FC reaction and the synthetic potential of quinones,[6] the preparation of substituted 2-cyclohexene-1,4-diones by

(1) For general reviews of Friedel−Crafts reactions, see: (a) *Organic Synthesis*; Smith, M. B., Ed.; McGraw-Hill: New York, 1994; p 1313. (b) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. Friedel−Crafts Alkylations. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 293−339. (c) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 733. (d) Roberts, R. M.; Khalaf, A. A. *Friedel−Crafts Alkylation Chemistry: A Century of Discovery*; Marcel Dekker: New York, 1984.

(2) For recent reviews on asymmetric Friedel−Crafts reactions, see: (a) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903–2915. (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550–556. (c) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190–2201.

(3) (a) Zhan, H.-B.; Liu, L.; Chen, Y.-J.; Wang, D.; Li, C.-J. *Adv. Synth. Catal.* **2006**, *348*, 229–235. (b) Yadav, J. S.; Reddy, B. V. S.; Swamy, T. *Synthesis* **2004**, 106–110. (c) Yadav, J. S.; Reddy, B. V. S.; Swamy, T. *Tetrahedron Lett.* **2003**, *44*, 9121–9124.

(4) For examples of protic acid catalyzed FC reaction, see: (a) Pirrung, M. C.; Park, K.; Li, Z. *Org. Lett.* **2001**, *3*, 365–367. (b) Pirrung, M. C.; Deng, L.; Li, Z.; Park, K. *J. Org. Chem.* **2002**, *67*, 8374–8388. (c) Pirrung, M. C.; Liu, Y.; Deng, L.; Halstead, D. K.; Li, Z.; May, J. F.; Wedel, M.; Austin, D. A.; Webster, N. J. G. *J. Am. Chem. Soc.* **2005**, *127*, 4609–4624.

(5) For a direct FC alkenylation in water without any added catalyst, see: Zhan, H.-B.; Liu, L.; Chen, Y.-J.; Wang, D.; Li, C.-J. *Eur. J. Org. Chem.* **2006**, 869–873.

(6) Thomson, R. H. *Naturally Occuring Quinones IV*; Blackie Academic & Professional: London, 1997.

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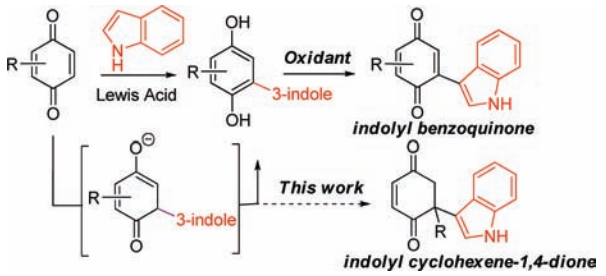
Scheme 1. FC Reaction of Indole with Benzoquinones



a classic FC alkylation with quinones still remains unsolved (Scheme 1). Substituted cyclohexene-1,4-diones and derivatives are found in a variety of bioactive natural products[7] and serve as excellent substrates for further synthetic elaboration. Recently, our group reported the synthesis and Diels–Alder reactions of 2-quinonyl boronic acids.[8] Our study evidenced a dramatic increase of their dienophilic reactivity when compared with other reactive quinones,[9] opening an easy access to otherwise elusive adducts, after a domino sequence of cycloaddition and protodeboronation. Herein, we describe the Friedel–Crafts alkylation of heteroaromatic compounds with 3-alkyl substituted 2-quinonyl boronic acids that enable a direct and site-selective heteroaromatic alkylation, to give 5-alkyl-5-heteroaryl substituted cyclohexene 1,4-diones.

We focused our study on 3-methyl substituted-2-quinonyl boronic acids **1**–**3**, available by CAN oxidation of the corresponding methyl-substituted 2,5-dimethoxy arylboronic acids, as previously reported.[8] Indole reacted with 3,5-dimethyl benzoquinonyl boronic acid **1** without any added catalyst, in CH_2Cl_2 (0.1 M) at room temperature to give, in 2 h, 6-(1*H*-indole-3-yl)-2,6-dimethyl-2-cyclohexene-1,4-dione **5a** in a 73% isolated yield (entry 1, Table 1). The FC alkylation of **4a** occurred by attack of the C3 indole to the methyl-substituted C3 carbon of **1**, generating a quaternary center, and was followed by in situ protodeboronation of the initially formed 1,4-adduct. The product was detected directly in the reaction vessel before workup by ^{1}H NMR.[10] FC reactions of indole with 2,6-dialkyl substituted quinones as electrophiles have been reported to give 2-indole-3,5-dialkyl substituted quinones.[3a,c] Our result illustrates the potential of the boron substituent as a temporary controller, opening up a straightforward and regiocontrolled access to the indole-substituted cyclohexenedienone adducts, not easily accessible by other methods. A significant increase of the electrophilic reactivity of quinone **1** at the methyl bearing carbon was evident.

Table 1. Friedel–Crafts Alkylation of Indoles **4** with **1**

entry	**4** (1.1 equiv) (R ≠ H)	time (h)	**5**	yield (%)
1	Indole	2	**5a**	73
2	R^1 = Me	5	**5b**	81
3	R^2 = Me	18	**5c**	89
4	R^4 = OMe	18	**5d**	92
5	R^5 = NHBOC	36	**5e**	70
6	R^4 = F	18	**5f**	83
7	R^4 = Br	72	**5g**	93
8[a]	R^3 = CO_2Me	3	**5h**	56

[a] Heat was applied (36 °C).

We later undertook a survey to know the scope of the reaction. We first considered the influence of indole architecture (Table 1). *N*-Methyl indole **4b** reacted similarly with **1** (CH_2Cl_2, rt, 5 h) to give compound **5b** (Table 1, entry 2, 81% yield). The reaction of 7-methylindole **4c** with **1** occurred more slowly, giving the addition/protodeboronation product **5c** in 89% yield (Table 1, entry 3). The incorporation of an electron-donating methoxy group at the C-5 position of the indole **4d** allowed the isolation of **5d** in 92% yield (Table 1, entry 4). The addition of 4-*N*-*tert*-butoxycarbonylamino indole to quinone **1** provided compound **5f** in 70% yield (Table 1, entry 5). The indole framework can also accommodate electron-withdrawing groups. Thus, 5-fluoro- or 5-bromoindole reacted with **1**, giving compounds **5f** and **5g** in 83% and 93% yield, respectively (Table 1, entries 6 and 7). 6-Methoxycarbonyl indole **4h** was less reactive, and complete evolution could only be achieved under reflux, affording **5i** in 56% yield (Table 1, entry 8).

Reactions of quinonyl boronic acid **1** with other heteroaromatic derivatives were next explored. As shown in Scheme 2, pyrrole was particularly reactive. When **1** and **6a** were dissolved in CH_2Cl_2 a mixture of the 2- and 2,5-dialkylated pyrrole derivatives **7a** and **8** in a 46:54 ratio was rapidly formed (Scheme 2). The monoalkylated product **7a** could be obtained in excellent yield (92%) using pyrrole as solvent. 2,4-Dimethylpyrrole **6b** behaves similarly, when reacted neat over 5 min, affording product **7b** in 56% yield.

Unfortunately, reactions of **1** with other heteroaromatic compounds under similar conditions failed even at long reaction times or high temperatures. To overcome this limitation, we screened different Lewis acids that might

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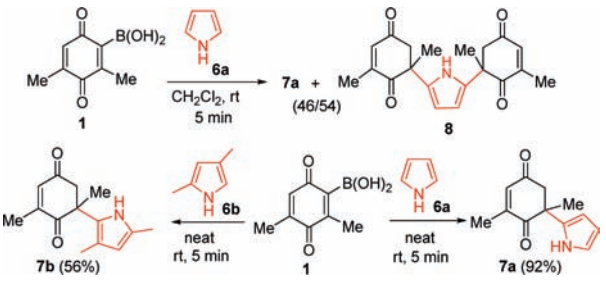
(9) (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698. (b) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1999**, *93*, 741–701. (c) Carreño, M. C.; Hernández-Torres, G.; Ribagorda, M.; Urbano, A. *Chem Commun.* **2009**, 6129–6144.

(10) Water is generated from the boronic acid/boroxine equilibrium presumably occurring in situ; see: Snyder, H. R.; Konecky, M. S.; Lennarz, W. J. *J. Am. Chem. Soc.* **1958**, *80*, 3611–3615.

Scheme 2. FC Alkylation of **6a** and **6b** with **1**



catalyze the Friedel−Crafts alkylation. The use of $Cu(OTf)_2$, ZnI_2, $Bi(OTf)_3$, $ZrCl_4$, $Yb(OTf)_3$, or $LiClO_4$ was ineffective. In contrast, catalytic $FeCl_3 \cdot 6H_2O$ (5 mol%) provided the desired alkylation products with full control of the regioselectivity and moderate to good yields. Thus, thiophene **6c** provided the 1,4-addition/protodeboronation product **7c** in 4 h and 69% yield in the presence of $FeCl_3 \cdot 6H_2O$ (Table 2, entry 1). Under the same conditions, 2-chloro-3-methylthiophene **6d** reacted in 48 h, leading to **7d** in 72% yield (Table 2,

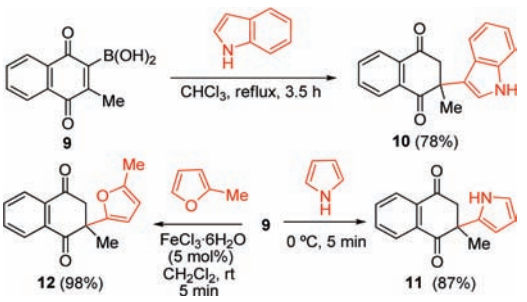
Table 2. FC Reactions of **6c−g** with **1** Catalyzed by $FeCl_3 \cdot 6H_2O$

entry	HetArH (6)	time	7	yield (%)
1		4 h	**7c**	69
2		48 h	**7d**	72
3		10 min	**7e**	69
4		18 h	**7f**	75
5		18 h	**7g**	47

entry 2). 2-Methyl furan **6e** reacted with **1** very quickly (10 min) to afford **7e** in 69% yield (Table 2, entry 3). 2,3-Dimethyl furan **6f** and benzofuran **6g** reacted similarly, giving derivatives **7f** and **7g** in 75% and 47% yields, respectively (Table 2, entries 4 and 5). In all cases, the heteroaromatic compound reacted, as expected, through its most electron-rich position.

(11) Previous to our work, there were two reports describing the FC reaction of indole with 2-methyl naphthoquinone in the presence of $Bi(OTf)_3$, to give, under similar reaction conditions, compound **10** in very different yields; see: Reddy, A. V.; Ravinder, K.; Goud, T. V.; Krishnaiah, P.; Raju, T. V.; Venkateswarlu, Y. *Tetrahedron Lett.* **2003**, *44*, 6257–6260 and ref 3c. We repeated both reactions under the conditions reported in both references to obtain a mixture of the starting 2-methylnaphthoquinone and the 1,4-addition product 10 (minor) in an 82:18 and a 96:4 ratio, respectively.

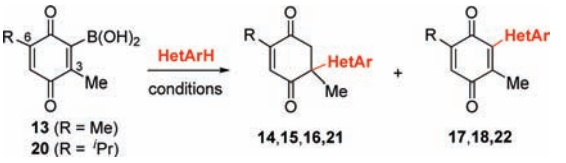
Scheme 3. FC Alkylation of Naphthoquinonyl Boronic Acid **9**

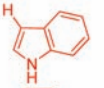
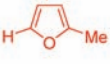
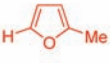


The generality of the FC reaction was further extended to the quinone partner. Thus, indole **4a** reacted with 3-methyl-2-naphthoquinonyl boronic acid **9** in refluxing $CHCl_3$, in the absence of any added catalyst, to afford the compound **10** in 78% yield (Scheme 3).[11] Once again, a very fast reaction (5 min) occurred between **9** and pyrrole (neat) at −20 °C, to give **11** in 87% yield. 2-Methylfuran reacted in the presence of catalytic $FeCl_3 \cdot 6H_2O$ to afford **12** in a short reaction time (5 min) and excellent yield (98%).

In the case of 3,6-dimethyl-2-benzoquinonyl boronic acid **13**, the reaction with pyrrole (neat) occurred at the C3 position of the quinone to give the quaternary alkylated product **14** in 74% yield (entry 1, Table 3).

Table 3. FC Reactions of Quinonyl Boronic Acid **13** and **20**



entry	HetArH	13 or 20	conditions	products yield (%)
1		**13**	neat,- 20 °C 5 min	**14** (74%)
2		**13**	CH_2Cl_2, rt, 18 h	**15/17** 84/16 (74%)
3		**13**	$FeCl_3 \cdot 6H_2O^a$ CH_2Cl_2, rt, 2 h	**16** (46%) **18** (17%)
4		**20**	$FeCl_3 \cdot 6H_2O^a$ CH_2Cl_2, rt, 2 h	**21** (46%) **22** (14%)

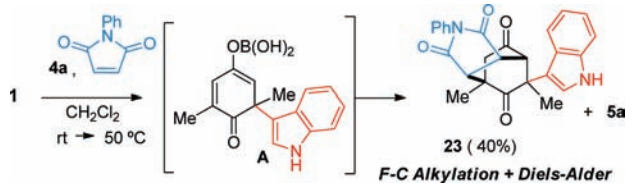
[a] 5 mol %.

The reaction between **13** and indole in CH_2Cl_2 gave an 84:16 mixture of compounds **15** (major) and indole quinone **17**, inseparable by column chromatography, in a 74% yield (entry 2, Table 3). A reaction between **13** and 2-methylfuran only occurred in the presence of $FeCl_3 \cdot 6H_2O$ (5 mol %), to afford a mixture of cyclohexenedione

16 and quinone **18**[12] that could be isolated in 46% and 17% yield, respectively (entry 3, Table 3).

The mechanism of the formation of the heteroaryl substituted quinones **17** and **18** was not evident. An *ipso*-substitution of the $B(OH)_2$ groups seemed plausible. To gain insight into this assumption, we synthesized an asymmetrically substituted analogue of **13**, 3-methyl-6-*iso*-propyl-2-quinonyl boronic acid **20**.[12] Its reaction with 2-methylfuran in the presence of $FeCl_3 \cdot 6H_2O$ (5 mol %) was completed in 2 h to give a mixture of compounds **21** and **22**, from which both were isolated pure in 46% and 14% yield, respectively (entry 4, Table 3). The formation of **22** supported the *ipso*-substitution process. Therefore, the heteroaromatic substituted benzoquinones **17**, **18** (see Table 3 and Scheme 4) should arise also from the direct substitution of the boronic acid by the heteroaromatic compound through an addition/elimination mechanism, favored by the presence of the vicinal carbonyl group.

Scheme 4. Domino FC/Diels−Alder Reaction/Protodeboronation between Indole **4a**, **1**, and *N*-Phenylmaleimide



The most general FC reaction of heteroaryl aromatic derivatives with our 3-methyl substituted 2-quinonyl boronic acids **1**, **9**, **13**, and **20** proceeded by nucleophilic attack of the heterocyclic compound at the C3 methyl substituted carbon. The boronic acid seems to be essential to trigger the process, since no reaction was observed between the pinacol ester derived from boronic acid **1**[8] and indole **4a** (CH_2Cl_2, rt, 5 d), under the conditions where the free boronic acid **1** reacted in 2 h. Moreover, the boron lacking 2,6-dimethylbenzoquinone was recovered unchanged when treated with indole **4a** under the same reaction conditions after long reaction times. These observations suggested that the enhanced electrophilicity of the quinonyl boronic acid must be a combination of the electron-withdrawing effect of the $B(OH)_2$ group, which decreases the LUMO energy of the C(2)=C(3) quinonic double bond, thus decreasing the HOMO−LUMO energy gap,[13] and the existence of a hydrogen bond between the boronic acid and the C-1 carbonyl group (see **1** in scheme of Table 1), evident in the X-ray of quinone **1**.[8b]

The results obtained suggest a domino process starting from the conjugate addition of the heteroaromatic compound to the quinone. The initial 1,4-adduct could suffer an in situ protonation and a transfer of the boron atom from carbon to oxygen to give a dienolate intermediate such as **A** (Scheme 4). To extend this domino sequence, we decided to trap the initially formed intermediate **A** by cycloaddition with *N*-phenylmaleimide. Thus, a mixture of 3,5-dimethyl-2-quinonyl boronic acid **1**, indole, and *N*-phenylmaleimide was dissolved in CH_2Cl_2. After 18 h a 57:43 mixture of **5a** and the polycyclic compound **23** was formed, from which **23** could be isolated pure in 40% yield as a 1:1 mixture of diastereoisomers. Compound **23** resulted from the domino process that embraces a Friedel−Crafts indole alkylation at C3 of the quinonyl boronic acid, a [4 + 2] cycloaddition reaction of the intermediate boron dienolate and a protodeboronation (Scheme 4). The formation of a mixture of epimers **23** must be a consequence of the *endo* approach of the dienophile from both faces of the intermediate diene **A**.

In summary, we have reported that 3-methyl substituted 2-quinonyl boronic acids are excellent electrophiles for Friedel−Crafts alkylation reactions of heteroaromatic compounds. The quinonyl boronic acids behave as highly reactive synthetic equivalents of quinones and allow direct access to the otherwise elusive HetArH 1,4-addition products to a methyl-substituted quinone double bond. The synthesis of 5-methyl-5-heteroaryl substituted cyclohexenediones was achieved in one step and good to excellent yields through a 1,4-addition reaction at C-3 and a spontaneous protodeboronation process. Our method allows an efficient and regioselective FC *alkylation* which is complementary to the typical quinone FC *alkenylation*. An initial synthetic extension of this method comprises a domino process including an FC alkylation/Diels−Alder reaction/protodeboronation.

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Supporting Information Available. Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via Internet at http://pubs.acs.org.

(12) See Supporting Information for details.

(13) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.